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## Iron deficiency and obesity: the contribution of inflammation and diminished iron absorption

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*Poor iron status affects billions of people worldwide. The prevalence of obesity continues to rise in both developed and developing nations. An association between iron status and obesity has been described in children and adults. The mechanism explaining this relationship remains unknown; however, findings from recent reports suggest that body mass index and inflammation predict iron absorption and affect the response to iron fortification. The relationship between inflammation and iron absorption may be mediated by hepcidin, although further studies will be required to confirm this potential physiological explanation for the increased prevalence of iron deficiency in the obese.*

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### INTRODUCTION

Iron is a nutritionally essential trace element that is critical for optimal physical and cognitive performance. Despite advances in the nutritional sciences and the development of worldwide economies, iron deficiency continues to be the most prevalent single micronutrient deficiency disease in the world, affecting billions of people.<sup>1</sup> The development of iron deficiency occurs in stages, beginning with the depletion of iron stores, followed by diminished iron transport, and finally the depletion of iron-containing proteins and enzymes, including hemoglobin, which results in iron deficiency anemia. The consequences of iron deficiency anemia are well described and include fatigue and diminished work capacity.<sup>2,3</sup> The consequences of iron deficiency without anemia are not as well described, but likely include diminished cognitive function and exercise performance.<sup>4–6</sup> In developed nations, iron deficiency and iron deficiency anemia tend to affect premenopausal women,<sup>7</sup> mainly through suboptimal iron intake and menstrual iron losses. In contrast, in developing nations, poor iron status occurs in most all population demographics, typically due to the lack of foods containing bioavailable iron.

Until recently, few studies had considered body weight or body composition as factors related to iron deficiency. Interestingly, a recent study, using data from the third National Health and Nutrition Examination Survey (NHANES III), determined that overweight American children were twice as likely to be iron deficient than normal-weight children,<sup>8</sup> and similar findings have since been reported in adults.<sup>9</sup> The association between iron status and obesity is one that should be explored further, as obesity and iron deficiency are diseases that continue to evolve worldwide, and both have significant public health implications.

### THE OBESITY EPIDEMIC

Obesity is a disease defined by an excess accumulation of body fat to the extent that health is adversely affected.<sup>10</sup> Within only a few decades, obesity has become a global public health concern. In the United States (US), the country for which the most comprehensive data is available, the prevalence of obesity has doubled over the past three decades;<sup>11</sup> data from 2005–2006 indicate that approximately 34% of US adults are obese.<sup>12</sup> The obesity epidemic is not limited to the United States; the

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prevalence of obesity is increasing in all regions of the world.<sup>10</sup> In 2005, an estimated 400 million adults worldwide were obese.<sup>13</sup> Furthermore, the prevalence of childhood overweight and obesity is increasing, with the worldwide prevalence having doubled or tripled in industrialized countries over the past few decades.<sup>14</sup> The same trends have been observed in developing countries. For example, the prevalence of adolescent and childhood overweight and obesity in children living in Egypt, Brazil, and Mexico has reached levels comparable to those seen in industrialized nations.<sup>14</sup> By 2010 an estimated one in seven children in the Americas and one in ten in the Eastern Mediterranean and European regions are predicted to be obese.<sup>14</sup>

With approximately one half of overweight adolescents and one third of children carrying excess weight into adulthood,<sup>15</sup> the global epidemic of obesity will continue to worsen. The public health implications of the obesity epidemic are staggering; obesity is associated with increased mortality from cardiovascular disease, diabetes, kidney disease, and some cancers.<sup>16</sup> In the United States alone, obesity was associated with 117 billion dollars in direct and indirect healthcare costs in 2000, and was the second leading cause of preventable death.<sup>17</sup>

### MAKING THE CONNECTION

The first reports of a potential connection between iron status and obesity appeared over 40 years ago.<sup>18,19</sup> These reports described lower serum iron concentrations in obese as compared to normal-weight adolescents. Very few studies pursued the reported connection between iron status and obesity until recently, when a series of investigations described an increased prevalence of iron deficiency in overweight and obese populations. The first of these, a cross-sectional study published in 2003, described a greater prevalence of iron deficiency, as indicated by serum iron levels <8 µmol/L, in overweight and obese Israeli children and adolescents.<sup>20</sup> Subsequently, a large study using data from the National Health and Examination Survey (NHANES III) confirmed those findings using multivariate regression analyses to demonstrate that overweight American children were twice as likely to be iron deficient than normal-weight control children.<sup>8</sup> In this study, iron deficiency was determined using a three-variable model, including cut-off values for transferrin saturation, free erythrocyte protoporphyrin, and serum ferritin.

The observations of a connection between iron status and obesity have since been extended to adults. Lecube et al.<sup>9</sup> reported that obese postmenopausal women had higher levels of soluble transferrin receptor (sTfR) than non-obese matched controls, and that body mass index (BMI) was positively associated with sTfR.

Recent studies have utilized sTfR as an indicator of iron status because this assay is not affected by the acute-phase response, as are other indicators of iron status, including serum ferritin.<sup>21</sup> Elevated sTfR levels are indicative of iron deficiency because erythrocytes in the bone marrow increase the presentation of membrane transferrin receptor in the presence of low levels of iron.<sup>22</sup> In another recent study, Menzie et al.<sup>23</sup> found significantly lower levels of serum iron and transferrin saturation (the ratio of serum iron to total iron binding capacity) in obese as compared to non-obese adult volunteers, and fat mass was shown to be a significant negative predictor of serum iron concentration. In a third study, using cut-off values for serum iron and sTfR, Yanoff et al.<sup>24</sup> confirmed an increased prevalence of iron deficiency in obese as compared to non-obese adults; in that study, serum iron was significantly lower and sTfR was significantly higher in the obese individuals. Similar to the Lecube et al.<sup>9</sup> and Menzie et al.<sup>23</sup> studies, this study uncovered significant correlations between serum iron, sTfR, fat mass, and BMI in adults. Collectively, these reports suggest that excess adiposity may negatively affect iron status.

### INFLAMMATION AND IRON ABSORPTION

Zimmermann et al.<sup>25</sup> recently studied unique populations to test the hypothesis that obesity may affect iron absorption through an inflammatory mediated mechanism. In these studies, women and children from transition countries, including Thailand, Morocco, and India, were utilized to investigate the relationship between BMI and iron absorption. Volunteers from transition countries were selected because these countries are undergoing rapid socioeconomic changes that have resulted in both malnutrition and overweight. For example, in Bangkok, Thailand, nearly 33% of women are overweight, and 24% are anemic.<sup>25,26</sup> Zimmermann et al.<sup>25</sup> refer to this circumstance as the "double burden" of the nutrition transition.

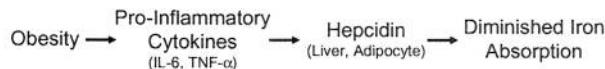
In the first experiment, 67 apparently healthy premenopausal Thai women were recruited to consume iron-isotope-labeled test meals and 25 women were recruited to serve as healthy controls. In this study, 22% of the women were considered overweight and 20% were iron deficient. The test meals, which consisted of foods typical to the Thai diet, contained approximately 4 mg of isotopically labeled fortification iron as [<sup>57</sup>Fe/<sup>58</sup>Fe]-ferrous sulfate. Prior to the meal, blood was analyzed for iron status indicators, including hemoglobin and serum ferritin. Inflammation was assessed using C-reactive protein. Fourteen days after the test meal a second blood sample was collected for the determination of isotope concentration and the calculation of iron absorption using mass spectrometry. The major finding was that after correcting for differences in initial iron status, multi-

ivariate regression indicated that fractional iron absorption was negatively correlated with C-reactive protein and BMI.

In the second experiment, Zimmermann et al.<sup>25</sup> combined data from four controlled efficacy trials of iron fortification using children from Morocco and India.<sup>27–29</sup> In these trials, responsiveness to iron fortification using iron salts, including encapsulated ferrous sulfate and micronized ferric pyrophosphate, was assessed in children and adolescents aged 5–16 years. The combined study population totaled 1688 children. Iron status indicators, including hemoglobin, serum ferritin, sTfR, and whole-blood zinc protoporphyrin (ZPP) were measured at baseline and following the 7–9-month fortification protocols. In these studies, the prevalence of overweight was 6%; this was lower than the prevalence reported in the adult study, although the prevalence of iron deficiency was higher, at 42%. The major findings indicated that in the combined baseline data, there was an inverse relationship between BMI Z-score and body iron, calculated from the serum ferritin/sTfR ratio. Furthermore, BMI was a significant negative predictor of body iron and a positive predictor of sTfR and ZPP at baseline, indicating that greater BMI was associated with degraded iron status. When considering the responsiveness to iron fortification, there was an inverse relationship between BMI Z-score and change in body iron. Greater BMI Z-score was a significant negative predictor of change in iron status, as assessed using the response of serum ferritin, sTfR, and ZPP. It should be noted that the association between greater BMI Z-score and change in serum ferritin was weaker than the relationship with the other iron status indicators, as serum ferritin may have been elevated in response to adipose-related inflammation, whereas other indicators, including sTfR, are not affected by inflammation.<sup>21</sup> The possible elevation in serum ferritin in response to inflammation may have also affected the relationship between BMI Z-score and body iron. Taken together, these studies confirm the association of diminished iron status with obesity; they also indicate, for the first time, that iron absorption is directly affected by inflammation and BMI. As such, these studies are among the first to identify the inflammatory response to obesity and increased body fat as a major effector of iron homeostasis in children and adults.

#### WHAT IS THE MECHANISTIC LINK BETWEEN BODY FAT AND POOR IRON STATUS?

If overweight and obese individuals are at greater risk for reduced iron absorption and iron deficiency, what is the mechanistic link between body fat and iron homeostasis? A number of hypotheses have been proposed, including increased plasma volume in the obese, the consumption



**Figure 1** Proposed mechanistic link between obesity and poor iron status.

of energy-dense, nutrient-poor foods,<sup>20</sup> and chronic inflammation in response to excess adiposity.<sup>24</sup> Few of these hypotheses have been explored in detail. The increased levels of both C-reactive protein and ferritin observed in the obese populations in the Yanoff et al.<sup>24</sup> study suggest that inflammation could contribute to diminished iron status. In the obese, serum ferritin is often elevated in response to inflammation, even in cases of iron deficiency; this highlights the utility of iron status indicators, including sTfR, which are not affected by the acute-phase response, for the identification of iron deficiency. The studies by Zimmermann et al. have provided important evidence that obesity influences iron absorption; however, the contribution to our understanding of the mechanism by which obesity affects iron status would have been improved by the direct assessment of pro-inflammatory cytokines and hepcidin in these studies.

#### Is there a hepcidin-inflammation connection?

Hepcidin is an important regulator of iron homeostasis, inhibiting iron absorption at the enterocyte and sequestering iron at the macrophage,<sup>30</sup> which could lead to decreased iron stores and hypoferremia. Obesity causes chronic inflammation,<sup>31</sup> which is associated with the expression and release of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). These pro-inflammatory cytokines may result in the release of hepcidin from the liver or adipose tissue.<sup>32,33</sup> The potential role of hepcidin in the development of iron deficiency in the obese is supported by the discovery of elevated hepcidin levels in tissue from patients with severe obesity, and the positive correlation between adipocyte hepcidin expression and BMI (Figure 1).<sup>32</sup> Even though the hepcidin-inflammation connection provides a succinct biological framework to explain the association of iron deficiency with obesity, additional research is required.

#### CONCLUSION

The independent consequences of iron deficiency and obesity have been well characterized. The recently described connection between iron deficiency and obesity is a cause for public health concern, as the combined impact of these nutritional comorbidities is unknown. Furthermore, the prevalence of obesity contin-

ues to climb in both developed and developing nations. As described in this manuscript, the inflammation associated with increased adiposity seems to be a mechanistic link between iron status and obesity. However, conclusive experiments establishing a direct connection between measured hepcidin levels, pro-inflammatory cytokines, and adiposity have yet to appear in the literature. The design and execution of these experiments, coupled with the development of appropriate cell and animal models,<sup>34</sup> will be critical to furthering understanding of the mechanistic relationship between iron status and obesity. Moreover, the understanding of this mechanistic relationship may allow for the development of nutritional and/or pharmacologic therapies that could prevent the development of iron deficiency in the obese.

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